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#### Amendment to CLAIMS

Claim 1 (Previously Presented): Use of one or more compounds having agonist activity to a 5-HT4 receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have the capacity of reducing pathological bronchocontraction 10 by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising the following 5-HT, receptor: agonists: benzamides containing the structural element 4-15 amino-5-chloro-2-methoxy benzamide based on metoclopramide, with the structural formula:

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having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

#### benzoic acid esters:

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preferably ML 10302, RS 57639, and SR 59768;
a 2,3-dihydro-bensofuran-7-carboxamide compound,

preferably ADR 932, Prucalopride (=R 093877), and SK-951;

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25 benzofuranes and benzotiophenes,

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ONH

NH<sub>2</sub>

the benzodioxan

the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone

e.g. preferably RS 67333 and RS 17017; naphtalimides, preferably RS 56532;

benzindolones;

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compounds in which the amide function has been replaced with an oxadiazol ring;

preferably YM-53389;

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benzimidazolone-1-carboxamides

preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236; the carboamides

indols, preferably 5-methoxytryptamine, 2-methyl35 serotonine, and 5-hydroxy-N,N-di-methyltryptamine;

compounds quaternized on the nitrogen in the side chain:

benzokinolinones

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5-carboxamidotryptamine (5-CT), with the structural formula:

$$H_2N$$
 $C$ 
 $CH_2$ 
 $CH_2$ 
 $CH_2$ 
 $CH_2$ 

3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-15 aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidineethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxy-20 methyl-4-pyrrolidinyl) benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzothiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, 25 zelmac,

, particularly

F N N N

## 2-piperidinmethylethers of bensimidazol

oxadiazalon based substance

kinolines

, particularly

and derivatives and pharmaceutically acceptable salts thereof.

Claim 2(Prevaily Presented): Use according to claim 1, wherein said compound is VB20B7, RS67333, BIMU 1, BIMU 8, 5-methoxytryptamine,

5 Zacopride, RS56532, Mosapride, BRL 24924, or SC 53116.

Claim 3 Previously Presented Use according to any one of the previous claims, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.

laim 4 (Previously presented): A method for treatment of disorders involving

bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a therapeutically effective amount of a compound according

'15 to any one of claims 1 and 2. .

tham 5 (Previously Presented). Use of one or more compounds having antagonist activity to a 5-HT3 receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT3 receptor in the manufacture of a me-

disament for therapeutic or prophylactic treatment of disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, wherein said compounds have

25 the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 5-HT<sub>3</sub> receptor antagonists

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### benzazepines, preferably mirtazapine

benztiazephines, preferably diltiazem

and fentiazines

preferably perphenazine, stemetil;

compounds also having  $5\text{-HT}_4$  receptor agonist activity, preferably benzamides

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(cisapride, zacopride, mosapride, pancropride, BRL 24924, BMY 33462)

10 and

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2,3-dihydro-benzofuran-7-carboxamides

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(preferably zatosetron=LY 277359, ADR 851);
 1,4-bensoxazin-8-carboxamides

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### preferably azasetron (=Y25130); benzimidazolones

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preferably itasetron (=DAU 6215);

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indazol-3-carboxamides

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preferably N 3389, LY 278584, DAT 582;

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wherein the latter group reminds most of the specific  $5\text{-HT}_3$  antagonists, which contains the group

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The grant of the Cathestone

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in different forms, such as

alosetron

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substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen

cilansetron

also being an antagonist against both 5-HT $_3$  and 5-HT $_4$  receptors,

#### bisindoles

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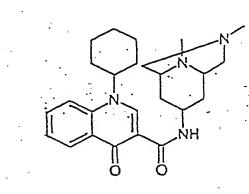
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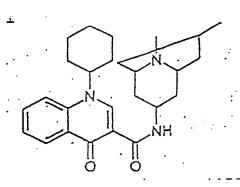
10 isoquinoline-1-ones

palonosetron (=RS 25259-197)

RS 42358-197

20 and the quinoline-3-carboxamides





30 WAY-SEC 579

Mirisetron (=WAY 100579),

quinoline-4-carboxylates

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preferably KF 17643

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preferably KF 18259;

'15 benzimidazolones

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preferably itasetron (DAU6215),

and the naphtimides

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35 preferably RS 56532;

RS 56532

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MDL 72222, which also is a specific  $5\text{-HT}_3$  antagonist;

; and

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GK 128

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Talipexole

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iodophenpropit

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thioperamide, and

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2-piperidin- and 2-piperazinbenzimidazoles; and also

(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1yl) -2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-10 ((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922, 20 KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2quinoxalinecarbonitrile, ONO-3051, Phenylbiquanide, 25 Pitozifen, Prochlorperazine, QICS 205-930, R(+) zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, 30 trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, QX 222; Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, 35 and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect,

and derivatives and pharmaceutically acceptable salts thereof.

- Claim 6 (Previously Presental): Use according to claim 5, wherein said compound is Tropanyl 3,5-dimethylbenzoate, MDL 72222, SDZ 216-525,
  - 5 ICI 169369, Zacopride, Tropisetron, Ramosetron, Ondansetron, Granisetron, Azasetron, Dolasetron, or Cilansetron.
- Jaim 1 (Previously Presented): Use according to any one of claims 5 and 6, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.
- Claim S(Neviously Presental: A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient suffering from asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease, a
  - ,15 therapeutically effective amount of a compound according to any one of claims 5 and 6.
- Claim 9 (Previously Presented): Use of a composition comprising a combination of at least one compound with agonist activity to the 5-HT, receptor, and at least one compound with antagonist ac-
  - 20 tivity to the 5-HT<sub>3</sub> receptor, for the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive
  - 25 pulmonary disease, preferably asthma and disorders related thereto.
- Haim 10 (Previously Presenta): Use according to claim 9, wherein said composition has the capacity of reducing pathological broncho-contraction by at least 30%, preferably at least 60%, and 30 most preferably at least 90%, and wherein said combina
  - tion is chosen from the following groups of
    - a) 5-HT<sub>4</sub> receptor agonists:

benzamides containing the structural element 4-amino-5-chloro-2-methoxy benzamide based on metoclopra

mide, with the structural formula:

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having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

#### benzoic acid esters:

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30 preferably ML 10302, RS 57639, and SR 59768;
a 2,3-dihydro-bensofuran-7-carboxamide compound,

3.5

preferably ADR 932, Prucalopride (=R 093877), and SK-951;

benzofuranes and benzotiophenes,

the benzodioxan

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the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone

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e.g. preferably RS 67333 and RS 17017; naphtalimides, preferably RS 56532;

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benzindolones;

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compounds in which the amide fuction has been replaced with an oxadiazol ring;

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preferably YM-53389;

benzimidazolone-1-carboxamides

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preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236; the carboamides

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indols, preferably 5-methoxytryptamine, 2-methyl-serotonine, and 5-hydroxy-N,N-di-methyltryptamine;

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compounds quaternized on the nitrogen in the side chain:

benzokinolinones

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5-carboxamidotryptamine (5-CT), with the structural formula:

$$H_2N$$
 $CH_2$ 
 $CH_2$ 
 $CH_2$ 
 $CH_2$ 
 $CH_2$ 

3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropyl-aminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidine-ethanol, arylcarbamate derivatives of 1-piperidine-nol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxy-methyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzo-thiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,

2-piperidinmethylethers of bensimidazol

...

oxadiazalon based substance

, particularly

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and serotonin (5-HT) and derivatives and pharmaceutically acceptable salts thereof.

#### b) 5-HT<sub>3</sub> receptor antagonists:

CI

benzazepines, preferably mirtazapine

### benztiazephines, preferably diltiazem

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#### and fentiazines

preferably perphenazine, stemetil;

compounds also having  $5-HT_4$  receptor agonist activity, preferably benzamides

<sup>′</sup> 15

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(cisapride, zacopride,
mosapride, pancropride,
BRL 24924, BMY 33462)

and

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WAY 100289

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2,3-dihydro-benzofuran-7-carboxamides

## (preferably zatosetron=LY 277359, ADR 851); 1,4-bensoxazin-8-carboxamides

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CI NON

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preferably azasetron (=Y25130);
 benzimidazolones

**(15** 

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preferably itasetron (=DAU 6215);

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indazol-3-carboxamides

30.

preferably N 3389, LY 278584, DAT 582;

wherein the latter group reminds most of the specific 5-HT<sub>3</sub> antagonists, which contains the group

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10 in different forms, such as

ondansetron

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25 alosetron

cilansetron

substances the structure of which has been inverted and the carbonyl group has been placed on the indoline nitrogen

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FK 1052

also being an antagonist against both  $5-HT_3$  and  $5-HT_4$  receptors,

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BRL 46470 A

bisindoles

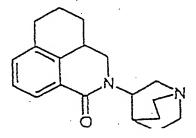
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isoquinoline-1-ones

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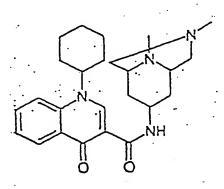


25 palonosetron (=RS 25259-197)

RS 42358-197

and the quinoline-3-carboxamides

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NH NH

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WAY-SEC 579

Mirisetron (=WAY 100579),

#### quinoline-4-carboxylates

10 preferably KF 17643

20 preferably KF 18259;

benzimidazolones

25 N O

preferably itasetron (DAU6215),

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and the naphtimides

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RS 56532 .

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preferably RS 56532;

MDL 72222, which also is a specific  $5\text{-HT}_3$  antagonist;

and

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GK 128

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Talipexole

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iodophenpropit

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thioperamide, and

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2-piperidin- and 2-piperazinbenzimidazoles; and also

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(R)-zacopride, 2-methyl-5HT, 3-(4-allylpiperazin-1yl) -2-guinoxalinecarbonitrile, 4-Ph-N-Me-guipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-862, Amitriptyline, Anpirtoline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdansetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKl-48903, ICS 205-930, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Mianserin, MK 212, N-3256, NAN-190, N-metylquipazin, 3-(1-piperazinyl)-2quinoxalinecarbonitrile, ONO-3051, Phenylbiguanide,

Pitozifen, Prochlorperazine, QICS 205-930, R(+) zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 10 216-525, Trimebutine, GR 65630, Tropisetron, L-683,877, and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect, and derivatives and pharmaceutically acceptable salts · 15 thereof.

- Claim II (Previously Presented): Use according to claim 10, wherein the composition comprises the following combinations of a 5-HT<sub>4</sub> receptor agonist and a 5-HT<sub>3</sub> receptor antagonist: VB20B7 and Tropanyl 3,5-dimethylbenzoate, VB20B7 and MDL 72222,
  - 20 RS67333 and Tropanyl 3,5-dimethylbenzoate, RS76333 and MDL 72222, VB20B7 and ICI 169369, RS67333 and ICI 169369, Zacopride and Tropanyl 3,5-dimethylbenzoate, Zacopride and MDL 72222, RS56532 and Tropanyl 3,5 dimethylbenzoate, RS56532 and MDL 72222, Itasetron and Tropanyl 3,5-
  - dimethylbenzoate, Itasetron and MDL 72222, VB20B7 and SDZ 216-525, and RS67333 and SDZ 216-525.
- Claim 12 (Previously Presental): A method for treatment of disorders involving bronchocontraction chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic
  - 30 bronchitis, and chronic obstructive pulmonary disease, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a composition according to any one of claims 10 and 11.
- Claim 13 (Previously Presenta): A method for treatment of disorders involving
  35 bronchocontraction chosen from the group consisting of
  asthma and disorders related thereto, emphysema, chronic

wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a 5-HT<sub>4</sub> receptor agonist according to any one of claims 1 and 2 and a 5-HT<sub>3</sub> receptor antagonist according to any one of claims 5 and 6, either simultaneously or sequentially.

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14-17 (canceled)

18. (new) Method of treating disorders involving human bronchocontraction, chosen from the group consisting of asthma and disorders related thereto, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease comprising:

administering one or more compounds having agonist activity to a 5-HT<sub>4</sub> receptor, wherein said one or more compounds have the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

19. (new) Method of claim 18, wherein said one or more compounds are chosen from the group comprising the following 5-HT<sub>4</sub> receptor agonists: benzmides containing the structural element 4-amino-5-chloro-2-methoxy benzamide, optionally having a basic nitrogen in a side chain from the amide nitrogen, said basic nitrogen often being a part of a sterically locked system, preferably BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, RO76186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, SDZ 216,454, TKS 159, Y-34959, YM-09151, YM-47813, and Zacopride;

benzoic acid esters:

preferably ML 10302, RS 57639, and SR 59768;

a 2, 3-diyhdro-bensofuran-7-carboxamide compound, preferably ADR 932, Prucalopride (=R 093877), and SK-951;

benszofuranes and benzotiophenes,

the benzodioxan

the benzoic acid antagonist RS 23597 (an ester) transformed to an agonist by conversion to a ketone

e.g. RS 67333 and RS 17017.

naphtalimides, preferably RS 56532;

benzindolones;

compounds in which the amide fuction has been replaced with an oxadiazol ring;

preferably YM-53389;

benzimidazolone-1-carboxamides

preferably BIMU 1, BIMU 8, DAU 6215, and DAU 6236;

the carboamides

Indols, preferably 5-methoxytryptamine, 2-methylserotonine, and 5-hydroxy-N,N-dimethyltryptamine;

Compounds quartenized on the nitrogen in the side chain:

bensokinolinones

5-carboxamidotryptamine (5-CT), with the structural formula:

$$H_2N$$
 $C$ 
 $CH_2$ 
 $CH_2$ 
 $CH_2$ 
 $CH_2$ 

5-HT, 3-Me-8-OH-DPAT, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), RS 23597-190, RS 67532, RU 28253, SB 204070, Bufotenine, 5-MeO-N,N,DMT, GR 113,808, α-methyl-5-HT, arylcarbamate derivatives of 1-piperidineethanol, arylcarbamate derivatives of 1-piperidineethanol, 4-amino-5-chloro-2-methoxybenzoic acid esters, 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide, thiophene carboxamide derivatives 3 (a-j), 5.azabicyclo(x.y.z) derivatives, 2-piperazinylbenzoxazole derivatives, 2-piperazinylbenzo-thiazole derivatives (e.g. VB20B7), Sandoz compound 1b, clebopride, 2-piperidinmethylethers of benzimidazole, zelmac,

2-piperidinmethylethers of bensimidazol

oxadiazalon based substance

, particularly

bensopyranes

and derivatives and pharmaceutically acceptable salts thereof.

- 20. (new) Method of claim 18, wherein said one or more compounds is VB20B7, RS67333, BIMU 1, BIMU 8, 5-methoxytryptamine, Zacopride, RS565323, Mosapride, BRL 24924, or SC 53116.
- 21. (new) Method according to claims 18-20, wherein said disorder involving bronchocontraction is asthma and disorders related thereto.